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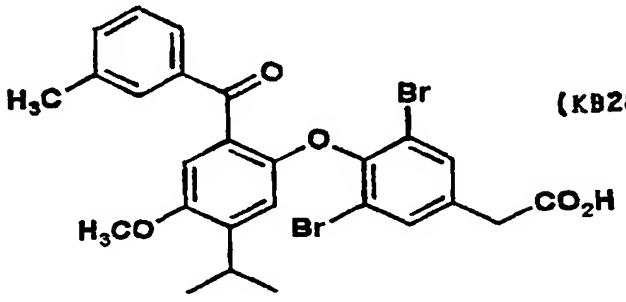

(KB285) (I)

(57) Abstract

Use of a liver–selective glucocorticoid antagonist, preferably the compound having formula (I) in the preparation of a pharmaceutical composition for the treatment of diabetes. A composition for the treatment of diabetes containing such a glucocorticoid antagonist, and a method of treating diabetes using the composition.

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TREATMENT OF DIABETES

Diabetes mellitus is one of the most serious medical problems in the western world where it affects around 5-6 % of the population. Diabetes is the leading cause of blindness in working adults in western countries, the most important cause of renal disease, and is associated with an increased risk for macrovascular disease, including heart attack, stroke and peripheral vascular disease. In the United States diabetes may afflict as many as 16,000,000 individuals and the cost for treating diabetes is over $100 billion annually.

Approximately 90% of all diabetics have non-insulin dependent diabetes mellitus (NIDDM or type 2 diabetes) and may or may not be dependent on exogenous insulin. Intensive treatment of the hyperglycemia of the other form of diabetes type 1 diabetes mellitus has been shown to markedly decrease the development of ocular, renal and neuropathic complications, and there is evidence that intensive treatment is also beneficial for type 2 diabetes. The available data also indicate that most patients are currently not receiving ideal and state-of-the-art treatment for either type 2 or type 1 diabetes. This inadequacy exists in spite of the availability of several different types of preparations of insulin for treatment of both type 2 and type 1 diabetes, and of a number of additional modalities, including agents that stimulate insulin release. e.g. sulfonylureas, influence liver glucose production. e.g. metformin, affect the sensitivity to insulin, e.g. troglitazone and promote glucose absorption e.g. α-glucosidase inhibitors. In spite of the availability of several different orally active agents that lower blood glucose levels, many patients with type 2 diabetes also require insulin for control of their blood sugar levels. Overall, insulin usage in type 2 diabetes exceeds that for type 1 diabetes, and there is general agreement that there is a need for additional orally active agents to treat type 2 diabetes.

A major problem with both type 2 and type 1 diabetes is that there is excessive and inappropriate production of glucose by the liver. This observation has been verified in many different laboratories studying a large variety of type 2 diabetes populations. This abnormality is the primary cause of fasting hyperglycemia and occurs in addition to defects in regulation of insulin release and in peripheral sensitivity to insulin. Thus, agents that

decrease liver glucose production would be beneficial for treating type 2 and perhaps also type 1 diabetes.

Therapy for non-insulin dependent diabetes mellitus (type 2 diabetes or NIDDM) remains inadequate in spite of a number of current treatment modalities. Despite the fact that increased glucose production plays a pivotal role in the pathophysiology of both fasting and postprandial hyperglycemia, there are no medical therapies, which have directly targeted this process in treatment of type 2 diabetes mellitus.

In spite of a number of current modalities to treat diabetes mellitus, none are ideal and problems with conventional treatments are summarised in Table 1 below:

Table 1

Class of compound	Mechanism of action	Efficacy (HbA1c)	Efficacy	Adverse effects	Comments
Insulin	Suppression of glucose production. Stimulate glucose utilization	Potentially normalize		Weight gain Hypo-glycemia	
Sulfonylureas	Increase insulin secretion	↓1.5-2.5%	Secondary failure	Weight gain Hypo-glycemia	Cardiac effects?
Biguanides	Suppression of glucose production	↓1.5-2.5%	Secondary failure	Diarrhea, Dyspepsia Lactic acidosis	
α-glucosidase inhibitors	Slow intestinal glucose absorption	↓0.5-1.0%	Modest efficacy	Flatulence Loose stools	
Thiazolidinediones	Improvement of insulin sensivitity	↓0.5-1.0%	Modest efficacy	Anemia Gastro-intestinal symptoms	Liver injury

Sulfonylureas such as glyburide and glypizide work primarily by stimulating pancreatic insulin release. They are relatively inexpensive and have been used with success. They have the disadvantage of being able to provoke hypoglycemia. In addition, the increased insulin release leads to more fat deposition and can provoke weight gain. They are also ineffective as monotherapy in many individuals.

Metformin and related products decrease liver glucose production by poorly understood mechanisms. Earlier studies suggested that the major mechanisms for the actions of these compounds are on gluconeogenesis. Later studies suggested that the compounds work

more by blocking glycogenolysis (degradation of stored glycogen). Previous problems with lactic acidosis with phenformin have largely been reduced with metformin. Nonetheless, metformin does produce anorectic effects. Whereas these compounds are being used as first line therapy, they nonetheless have limited effectiveness.

The major mechanism of action of troglitazone and other thiazoladinediones (insulin sensitisers) is to improve the sensitivity to insulin in peripheral tissues, such as muscle and fat, without stimulating insulin release. These actions can also decrease liver glucose production to a small degree. These drugs also lower blood pressure and tend to produce favourable effects on lipid profiles. A disadvantage is their limited effectiveness in restoring blood glucose to normal levels, such that many patients require additional therapy. Recently, there have been several reports of liver injury associated with troglitazone.

Carbohydrate absorption inhibitors α-glucosidase inhibitors, e.g. acarbose, block the enzymatic generation and absorption of glucose in the gastrointestinal track. Thus, they are mostly effective on reducing postprandial glucose levels. They have limited effectiveness, and side effects of flatulence, soft stools and diarrhoea can occur.

Glucocorticoids, of which cortisol is pre-eminent in humans, steroids which are secreted by the adrenal glands under normal physiological circumstances. Secretion is dramatically increased in response to a great variety of different stress conditions. One effect of glucocorticoids is to enhance glucose production in the liver by promoting gluconeogenesis, which is the biosynthesis of glucose from non-glucose precursors, including glycerol, alanine and pyruvate, and is distinct from the breakdown of glycogen. Thus, in glucocorticoid insufficiency there is a tendency to hypoglycemia, with decreased liver glucose production. Further, development of Addison's disease in the diabetic generally leads to lowered glucose levels. Conversely, glucocorticoid excess can provoke frank diabetes in individuals with latent diabetes mellitus, and generally aggravates glycemic control in established diabetics. Similar influences have been observed in various animal models. Increased glucose production in glucocorticoid excess states can precipitate latent diabetes mellitus or aggravate existing diabetes. Conversely, in

glucocorticoid deficient states, there is decreased glucose production, and a tendency to hypoglycemia. Previous efforts to block glucocorticoid action in diabetes have been hampered by the fact that any compounds used would generally block glucocorticoid action in all tissues and would lead to the potential problems of glucocorticoid insufficiency, such as hypotension, shock and ultimately death during stress conditions.

To date, all means to block glucocorticoid action have been generalized throughout the body rather than selective in the liver. Thus, adrenalectomy leaves the patient with frank adrenal insufficiency and the problems of Addison's disease. Blockade of adrenal steroid production, for example by metyrapone, or of glucocorticoid action, for example with RU486 can be of limited duration of effectiveness, since long term, compensatory ACTH hypersecretion with increased cortisol release can sometimes override the block. Even when these modalities are effective, they result in generalized adrenal insufficiency. The increased glucose production in response to glucocorticoids is due to effects on a number of proteins. Important among these are effects on various transaminases, such as tyrosine aminotransferase and aspartate aminotransferase, that convert amino acids to glucose precursors, and induction of glucose-6 phosphatase and phosphoenolpyruvate carboxy-kinase (PEPCK). Even a modest increase of PEPCK, as obtained in transgenic mice, gives rise to hyperglycemia. In mice with type 2 diabetes and increased levels of corticosterone (the endogenous glucocorticoid of that species) it has been found that there is increased expression of PEPCK. The inventors have found that this overexpression of PEPCK can be repressed by treatment with the GR antagonist RU486 with a concomitant decrease in the hyperglycemia.

According to one aspect of the invention, there is provided a method of treating diabetes, the method comprising lowering or preventing expression of an enzyme selected from PEPCK, glucose 6 phosphatase or a transaminase by treatment of the subject with a liver-selective glucocorticoid antagonist, that is to say one which acts to prevent or reduce glucose production in the liver. A liver-specific GR antagonist would not have problems or non-specific glucocorticoids, should counteract the increased liver glucose production in diabetes mellitus and should be useful for treatment of type 2 diabetes.

The liver selective GR antagonist of the present invention offer a number of benefits. First, it would decrease liver glucose production. This action should have a significant effect on glycemic control in view of the important role played by excessive liver glucose production in maintaining hyperglycemia type 2 diabetes. Second, such a drug should enhance insulin sensitivity because of the overall improvement in the metabolic milieu and the amelioration of the hyperglycemia-induced defects in insulin action and secretion. The decreased demand on β-cell secretion, as a result of a reduction in glycemia, might retard the progressive β-cell dysfunction characteristic of type 2 diabetes. Other benefits of a GR antagonist are that such a drug would not be expected to cause hypoglycemia and, it may be used either as a mono-therapy or in combination with existing therapies. In general, conventional oral agents are contraindicated for patients who are seriously ill or have significant kidney or liver disease. Depending on the mechanisms of its clearance, a liver selective GR antagonist would be useful in some of these situations (e.g. stress induced diabetes).

The use of insulin in type 2 diabetes patients is predicated on the severity of the disease. A GR antagonist can be utilized to reduce or eliminate the need for insulin injections in many patients. Furthermore because of its unique mechanism of action a GR-antagonist may be effective either alone or in combination with existing oral anti-diabetic medications. Moreover, glucose intolerance is part of a metabolic syndrome that can also include abdominal obesity, hypertension and hyperlipidemia. An orally administered GR antagonist may be of value in reducing glucose intolerance. The design of liver selective glucocorticoid antagonists may be under taken by the skilled worker using several approaches. These include the design of compounds that are metabolized to an inactive derivative in the liver (first pass destruction), are specifically taken up by the liver, and/or have specificity in terms of how they act on specific response elements.

For determining glucocorticoid action cells such as CHO (Chinese hamster ovary) cells stably transfected with vectors that express human GR and a glucocorticoid inducible reporter gene vector containing glucocorticoid response elements coupled to alkaline phosphatase (ALP) coding sequences can be used. In this case, ALP gene expression is transcriptionally activated in a glucocorticoid-dependent fashion in these cells.

The ALP reporter protein is secreted into the medium and its activity can be determined indirectly by a chemoluminescence assay making this reporter assay very sensitive compared to the commonly used chloramphenicol acetyl transferase (CAT) or luciferase assays. Assays may be established to assess GR activities with the various different glucocorticoid response elements and promoter contexts. These assays may include the use of several different types of glucocorticoid response elements (GREs) and promoter contexts that are used by cells to mediate glucocorticoid responses. They also recognize that GR interaction with other proteins, such as the activator protein-1 (AP-1) complex, rather than DNA are frequently employed to tether the GR to proteins involved in transcription control.

Finally, several different types of cells, reflective of important glucocorticoid responsive tissues may be used in the determination glucocorticoid responsiveness. Preferably, these cell lines are stably transfected such that GR levels near to the physiological are employed. Liver cell lines are particularly useful for the study of glucocorticoid antagonists on glucocorticoid regulated functions relevant to diabetes are liver cell lines. Measurements can be made in these cells of gluconeogenesis and glycogen deposition, and of specific enzymes involved in glycogen production and degradation, and gluconeogenesis.

Various animal models for *in vivo* testing of new compounds e.g. ob/ob mouse (a model of obese diabetes), and GK-rats (a model of non-obese diabetes). In these animals, studies may be performed to evaluate insulin release, insulin sensitivity and glucose turnover. Insulin sensitivity may be estimated by a hyper insulinemic / euglycemic clamp, while glucose turnover is studied using 6-H^3 glucose. In addition many *in vitro* models are available such as the isolated islets, isolated perfused rat pancreas perifused islets, patch clamp techniques, islet ion fluxes and isolated perfused rat liver.

The effect of liver selective glucocorticoids antagonistic on gluconegenesis in man such as evaluation of glucose turnover with help of tracers, insulin sensitivity, with clamps and insulin requirement with the use of an artificial pancreas.

It should be noted that even though numerous agents are currently available, none of them addresses adequately the issue of glucose toxicity in the liver caused by increased glucose

production in the liver. A liver-selective GR antagonist should be an important addition to the therapeutic arsenal for use as either front line therapy or as adjunctive therapy to currently available drugs.

We propose that the most important contributing factor in the many complications of elevated blood glucose levels is the excess production of glucose in the liver. Liver is the primary organ of the body where glucose is produced from non-sugars. The liver determines the level of fasting glucose and accounts for 50% of postprandial glucose disposal. The only drug available today that effects hepatic glucose production is metformin. Metformin's mechanism of action is unknown, it is moderately effective and its effect wanes over time, and it has toxicities. A liver-selective GR antagonist have greater impact on the liver and its mechanism at the cellular level will be well defined.

Clinically, therapy begins with normalizing of the fasting level of glucose. The livel selective glucocorticoid antagonists of the present invention are the first drug specifically acting on the liver to accomplish the goal of controlling fasting hyperglycemia

It is now recognized that while regulation of glucose production by hormones and substrates can occur in type 2 diabetes, such regulation is operative at a higher "set-point". Thus, higher levels of circulating insulin and glucose are necessary to maintain glucose production at a near-normal level. It is likely that the level of gene expression and the activity of key enzymes, such as PEPCK and glucose-6-phosphatase, largely determine interindividual variations in this set point.

Further benefits confered by the method of the present invention include restoration and maintenance of normal blood glucose levels both in patients with impaired glucose tolerance (IGT), and in the diabetic patient for all levels of severity of type 2 diabetes, i.e. monotherapy, in combinations, and as a means of eliminating insulin.

Prevention and failing that, at least a delay in the development of macrovascular and microvascular complications of diabetes, is a key to improved therapy. Preservation of normal β-cell function in the pancreas and avoidance of abnormalities in blood glucose

and insulin levels help to achieve these objectives. Improvement of insulin sensitivity, which prevents the deterioration in an individual's quality of life, is important but it does not by itself address the problem of glucose toxicity.

Compositions and methods of treatment in accordance with the invention will now be described, by way of example only, with reference to the accompanying drawings Figs. 1 to 3 in which:

Fig. 1 illustrates the GR antagonist effects of a compound in accordance with the invention in GRAF cells;

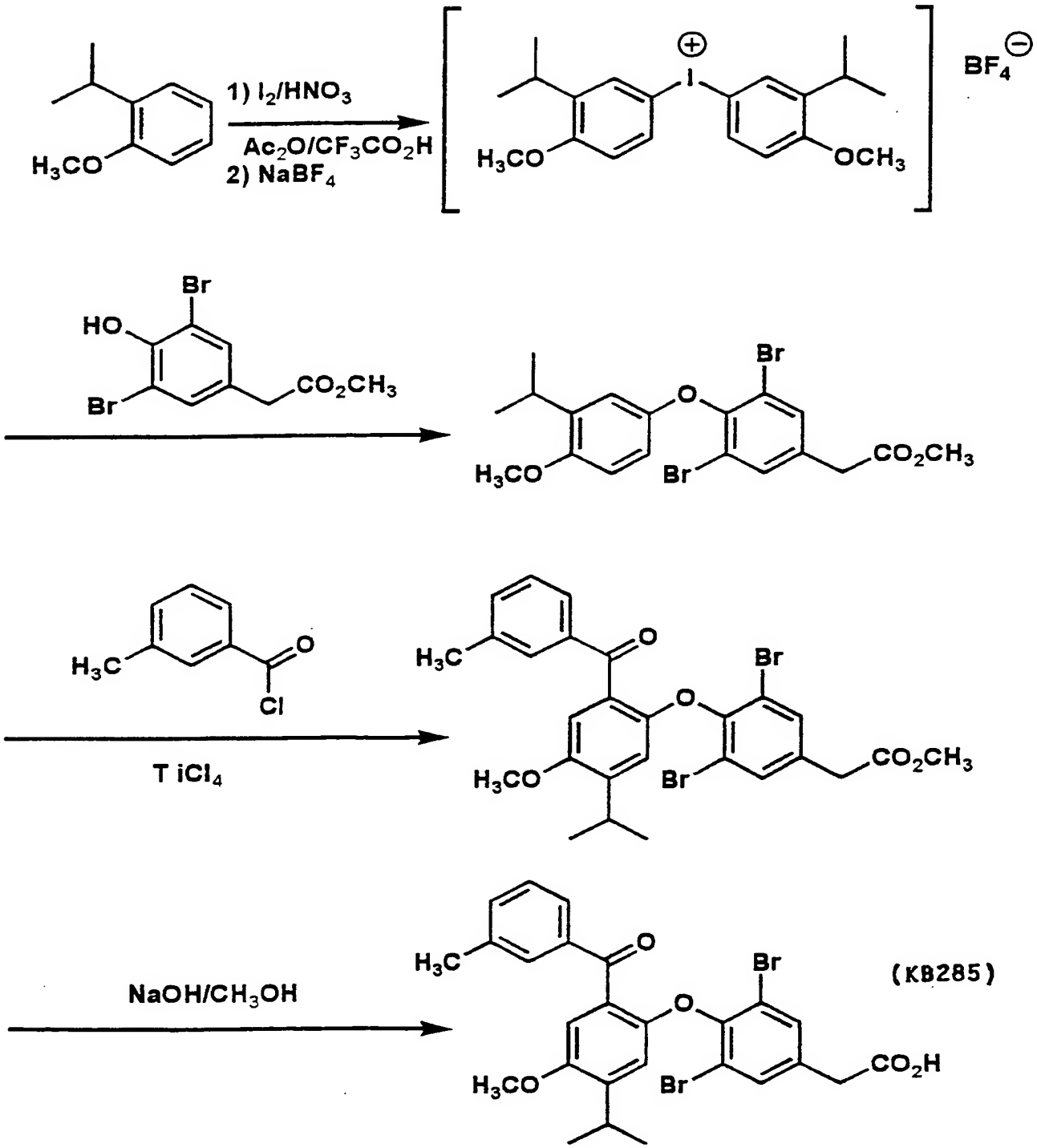
Fig. 2 illustrates the GR antagonist effects of a compound in accordance with the invention in liver cells; and

Fig. 3 illustrates the effects of a compound in accordanced with the invention on fasting glucose and corticosterone serum levels in mice.

In these examples, the compound {3,5-dibromo-4-[5-isopropyl-4-methoxy-2-(3-methyl-benzoyl-phenoxy] phenyl}-acetic acid, herein referred to as "KB285" was shown to be a glucocorticoid antagonist and to reduce gluceonogenesis *in vitro*. *In vivo*, the compound was shown to lower blood glucose levels after fasting.

EXAMPLE 1 :

The compound KB285 was synthesized as follows



{3,5-Dibromo-4-[5-isopropyl-4-methoxy-2-(3-methyl-benzoyl)-phenoxy] phenyl}-acetic acid

(a) bis(3-isopropyl-4-methoxy-phenyl)iodonium tetrafluoro borate. Fuming nitric acid (24.8 mL, 530 mmol) was added dropwise to 62.8 mL of acetic anhydride at -20° C. Iodine (22.6 g, 88.8 mmol) was added in one portion followed by drop wise addition of trifluoroacetic acid (41 mL, 532 mmol). The mixture was stirred at room temperature until all the iodine dissolved. Nitrogen oxides were removed by purging with nitrogen. The reaction mixture was evaporated, the residue was dissolved in 252 mL of acetic anhydride and cooled to -20° C. To the stirred mixture 2-isopropylanisole (80 g, 530 mmol) in 300 mL of acetic anhydride and 45.2 mL of trifluoroacetic acid was added dropwise. The mixture was stirred at room temperature overnight and then evaporated. The residue was dissolved in 300 mL of methanol and treated with 300 mL of 10% aqueous sodium bisulfite and 2 liter of 2M aqueous sodium borotetrafluoride. After the precipitate had aggregated, petroleum ether was added and the supernatant was decanted. The precipitate was triturated with petroleum ether, filtered, washed with petroleum ether and dried at room temperature under vacuum to give 65 g (71%) of bis(3-isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate as a white solid. (Naokata Yokoyama, Gordon N. Walker, Alan J. Main, James L. Stanton, Michael M. Morrissey, Charles Boehm, Allan Engle, Alan D. Neubert, Jong M. Wasvary, Zouhair F. Stephan and Ronald E. Steele, *J. Med. Chem.*, **38**, 695, (1995)).

(b) [4-(2-Benzoyl-5-isopropyl-4-methoxy-phenoxy)-3,5-dibromo-phenyl]-acetic acid methyl ester. To a stirred mixture of bis(3-isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate (1 g, 3,1 mmol) and copper bronze (0.38 g, 6.0 mmol) in CH_2Cl_2 (7 mL) at 0° C was added a mixture of (3,5-Dibromo-4-hydroxy-phenyl)-acetic acid methyl ester (1g, 3.1 mmol) and triethylamine (0.375 g, 3,7 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred in the dark for five days and filtered through silica gel. The filtrate was evaporated and the residue purified on a chromatotoron (silica, 9:1 n-heptane/ethyl acetate) to give 1.11 g (76%) of [4-(2-Benzoyl-5-isopropyl-4-methoxy-phenoxy)-3,5-dibromo-phenyl]-acetic acid methyl ester as a white solid.

(c) {3,5-Dibromo-4-[5-isopropyl-4-methoxy-2-(3-methyl-benzoyl)-phenoxy] phenyl}-acetic acid methyl ester. To a stirred mixture of 4-(3-isopropyl-4-methoxyphenoxy)-3,5-dibromo-benzoic acid methyl ester (50 mg, 0.11 mmol) and 3-methyl-benzoylchloride (82mg, 0.53 mmol) in CH_2Cl_2 (1 mL) was added titanium tetrachloride (100 mg, 0.53 mmol) drop wise. The mixture was stirred for two days at room temperature and poured over ice. The aqueous phase was extracted with EtOAc and the organic phase was dried over $MgSO_4$, filtered and evaporated. The crude product was purified on a chromatotron (silica, 8:2, n-heptane/ethyl acetate) to give 52 mg (83 %) of {3,5-Dibromo-4-[5-isopropyl-4-methoxy-2-(3-methyl-benzoyl)-phenoxy] phenyl}-acetic acid methyl ester as a white solid.

(d) {3,5-Dibromo-4-[5-isopropyl-4-methoxy-2-(3-methyl-benzoyl)-phenoxy] phenyl}-acetic acid. {3,5-Dibromo-4-[5-isopropyl-4-methoxy-2-(3-methyl-benzoyl)-phenoxy] phenyl}-acetic acid methyl ester (25 mg, 0.04 mmol) was dissolved in 0,5 mL of methanol. 0.3 mL NaOH (1 M, aq) was added and the mixture was stirred at room temperature for 16 h. The reaction was acidified with 1M HCl at 0° C, evaporated and extracted with EtOAc. The extract was dried over $MgSO_4$, concentrated and dried under vacuum to give {3,5-Dibromo-4-[5-isopropyl-4-methoxy-2-(3-methyl-benzoyl)-phenoxy] phenyl}-acetic acid 19 mg (80 %) as a white solid. ^1H NMR ($CDCl_3$) δ7.80(m, 2H), δ7.42(s, 2H), δ7.33(m, 2H), δ6.98(s, 1H), δ6.24(s, 1H), δ3.80(s, 3H), δ3.57(s, 2H), δ3.22(m, 1H), δ2.37(s, 3H), δ1.07(d, 6H).

EXAMPLE 2 : Receptor Binding

The results show the glucocorticoid receptor that KB285 binds to GR with similar binding affinity as dexamethasone. The IC_{50} for dexamethasone is 9.1 nM and the IC_{50} for KB285 is 19 mM (see Table 2). Using similar binding competition assays for the progesterone, mineralocorticoid and androgen receptors, we have shown that KB285 has very low binding affinity to these receptors (Table 2).

The cytosol from Sf9 cells, expressing either androgen receptor (AR), glucocorticoid receptor (GR), mineralocorticoid receptor (MR) or progesterone receptor (PR), was incubated for 16-18h at 4°C with [^{3}H]-steroid in presence of increasing concentrations of unlabelled ligand. The unlabelled ligand was diluted in DMSO which resulted in a final concentration of DMSO of 4.3% [^{3}H]-aldosterone, [^{3}H]-dexamethasone, [^{3}H]-mibolerone and [^{3}H]-R5020 was used as tracer with MR, GR, AR and PR respectively. Corresponding non-radioactive ligand was used as a control. Receptor bound and unbound ligands were separated with Sephadex G25 columns (QS-2A). Receptor bound radioactivity was measured with RackBeta (Wallace Oy).

Receptor/labelled ligand	**Reference/ Compound**	**IC_{50} (nM)**	**log IC_{50}**
hGR/^{3}H-dex	Dexamethasone/	9.1	-8.0416
	KB285.2	19	-7.7136
hPR/^{3}H-R5020	R5020/	2.9	-8.5329
	KB285.2	3800	-5.4175
rMR/^{3}H-aldo	Aldosterone/	6.6	-8.1785
	KB285.2	2400	-5.6272
hAR/^{3}H-mib	Mibolerone/	3.8	-8.4154
	KB285.2	5500	-5.2605

Table 2

EXAMPLE 3 : Cell based asays

In glucocorticoid reporter cell line GRAF cells, KB285 was shown to have antagonistic effect, IC_{50} = 0.4 μM, but no agonistic effect. The dlose response curve of Figure 1 shows

that the compound can inhibit a dexamethasone-stimulated increase in the expression of alkaline phosphatase (ALP), the reporter gene with an IC_{50} of 0.4 μM.

Specifically the compounds KB283 AND RU486 were tested in GRAF cells which are CHO-K1 cells stably transfected with pMT-hGR and the reporter vector pMMTV-ALP (Alksnis, M *et al.* (1991) *J. Biol. Chem.* **266**: 10078-10085, Nilsson *et al.* (1994) Advances in Steroid Analysis '93, "Proceedings of the 5th Symposium on the Analysis of Steroids", Ed. G`r`g S. Published by AkadJmiai Kiad\, Budapest, Hungary, p. 57-67). Cells were routinely cultured in Ham's F12 medium in the absence of phenol red but supplemented with 10% fetal calf serum. Cells were induced for 46 h in opti-MEM with the indicated compound concentrations. Secreted alkaline phosphatase activity was analyzed in the cell medium by a chemiluminescence assay essentially as described in Tizard, R *et al.* (1990) *Proc. Natl. Sci.* U.S.A. **87**: 4514-4518 and Nilsson *et al* (1994) (*Supra*).

In liver-derived H4IIE cells (Hepatoma cells, TAT assay); KB285 also shows antagonistic effects, IC_{50} = 2.5 μM and the compound also shows no agonistic effect.

Specifically H4IIE cells were routinely cultured in MEM supplemented with 10% FCS, 1% non essential aminoacids and 2 mM L-glutamine. For treatment 0.75 x 10^6 cells per well were seeded into 96-well plates. After 24h, the medium was replaced by MEM supplemented with 1% DCCFCS (FCS stripped with dextran-coated charcoal), and compounds were added for 24h. TAT activity was modified from Diamondstone . T. I. *et al.* (1996) Anal. Biochem **16**, 395-401 to be measured in 96-well plates.

KB285 showed antagonistic activity in the TAT (tyrosine aminotransferase) assay performed on the hepatoma H4IIE cells. As shown in Fig. 2, KB285, can antagonise the dexamethasone-induced increase in TAT activity in a dose dependent way, with an IC_{50} of 2.5 μM. The compound shows no agonistic effect (Fig. 2).

EXAMPLE 4 : In vivo testing in db/db mice

Male C57BL/Ks J Rj-db/db mice were obtained from Centre d'Ilevage R. Janvier, Le Genesr-St-Isle, France. All animals were housed in standard animal cages, had free access

to water, and were fed *ad libitum* with a normal laboratory chow. The mice used for experiments were 7-8 weeks old and 5 animals per treatment were used. Drug dosages in the experiments were 8, 25 and 75 mg/kg and the compound were prepared for oral administration as a suspension in sterile water supplemented with 1% hydroxylethylcellulose and 1% Tween 80. Mice were given two administrations, first dose at 4.30 pm and second dose at 8.00 am. Animals were fasted 4 h before blood sampling. Blood samples were collected from vehicle and compound treated animals by cardiac puncture under isoflurane anaesthesia at 12.30 pm.

KB285 was found to reduce the fasting serum glucose levels in the db/db mice. The glucose lowering effect is 62% compared to vehicle control at a dose of 25 mg/kg. The reference substance RU486 shows a glucose lowering effect of 33% at a dose of 75 mg/kg (Fig. 3). Corticosterone is used as a marker for systemic glucocorticoid effects. RU486 shows an increase in the corticosterone levels (584 ng/ml) compared to vehicle control (301 ng/ml). This is due to systemic effects of RU486. The effect of KB285 is less prominent with a corticosterone level of 360 ng/ml (Fig. 3). This indicates that KB285 has reduced side effects/systemic effects compared to RU486.

Results:

Compound	Dose mg/kg	glucose g/l	corticosterone ng/ml
KB 000285	8	2.66±1.57	386 ±49.4
	25	1.44 ±0.37	364 ±42
	75	2.72 ±.79	436 ±
Vehicle	-	3.81 ±1.52	301 ±34.5

Claims

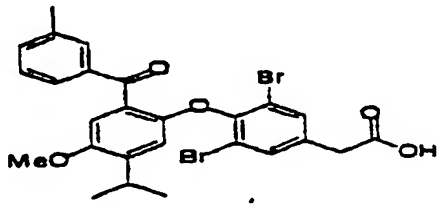
1. The use of a liver-selective glucocorticoid antagonist in the preparation of a pharmaceutical composition for the treatment of diabetes.

2. The use of a liver-selective glucocorticoid antagonist in the preparation of a pharmaceutical composition for the control of a glucocorticoid regulated gene expression in extra hepatic tissues.

3. The use of a glucocorticoid antagonist according to claim 1 in which the diabetes is type 2 of diabetes or Impaired Glucose Tolerance.

4. The use of glucocorticoid antagonist according to claim 1 in which the diabetes is type 1 diabetes.

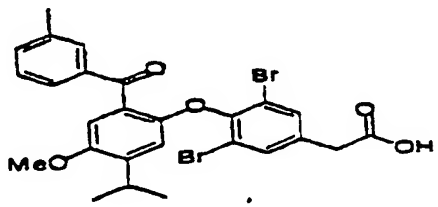
5 Use according to any of claims 1 to 4 wherein the selective glucocorticoid antagonist is



(KB285)

6. A composition for the treatment of diabetes comprising at least one liver-selective glucocorticoid antagonist .

7. A composition according to claim 6 in which the glucocorticoid antagonist is



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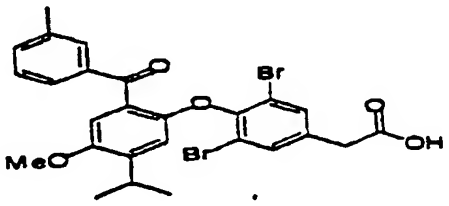
8. A composition according to claim 6 in which the glucocorticoid antagonist has an affinity for the glucocorticoid receptor of less than 10^{-6} M.

9. A composition for the treatment of diabetes according to claim 6, 7 or 8 and at least one other compound selected from insulin, sulfonylureas, biguanides, α-glucosidase inhibitors and thiazolidinediones, PPAR γ agonists.

10. A method of treating diabetes comprising lowering or reducing expression of at least one liver enzyme selected from PEPCK, glucose 6 phosphatase, and transaminases by treatment with a liver selective glucocorticoid antagonist.

11. A method according to claim 10 in which the liver-selective glucocorticoid antagonist is



(KB285)

12. A method according to claim 10 or claim 11 in which the transaminase is glucocorticoid regulated and expressed in the liver.

13. A method according to claim 12 in which the transaminase is tyrosine aminotransferase or aspartate aminotransferase.

Fig1.

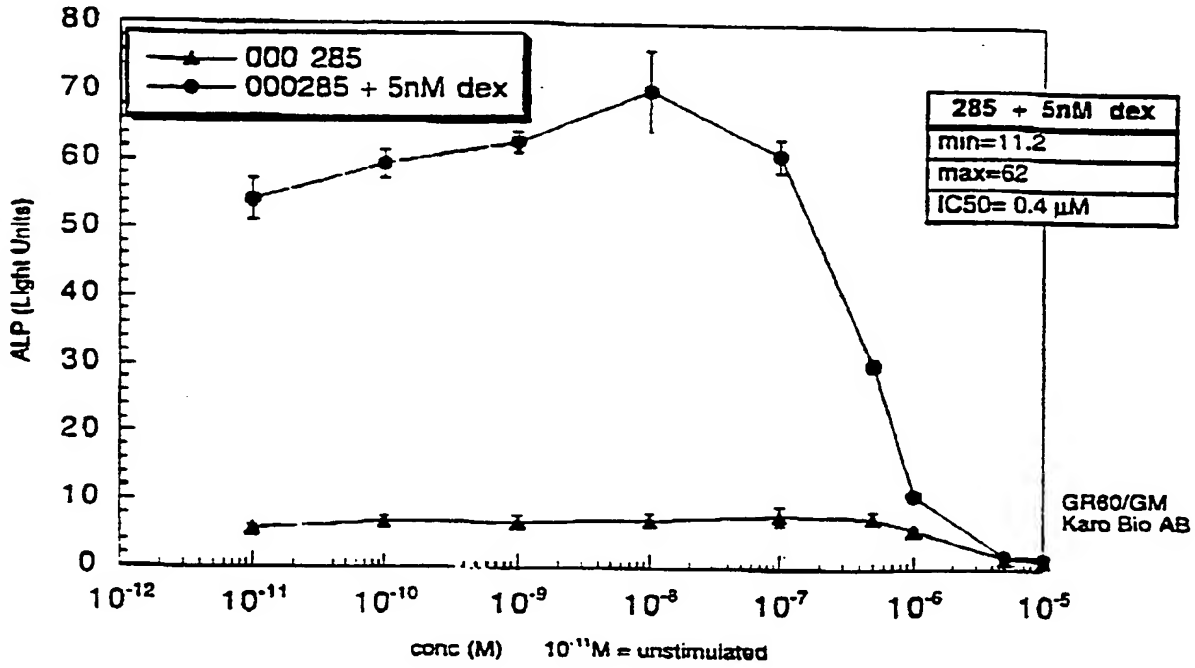


Fig2

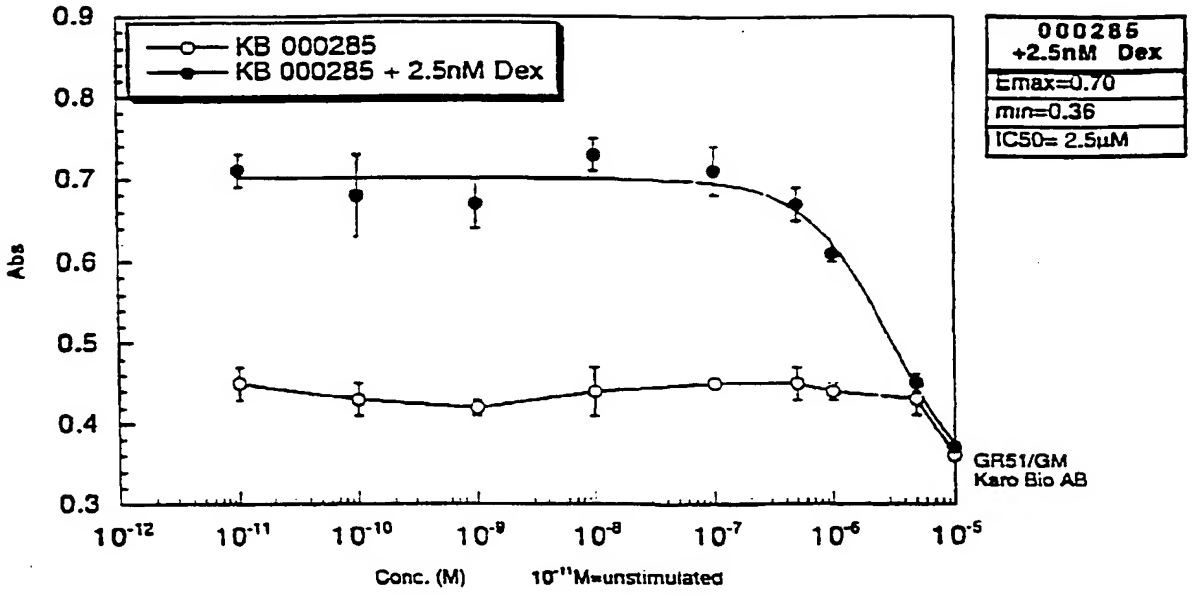
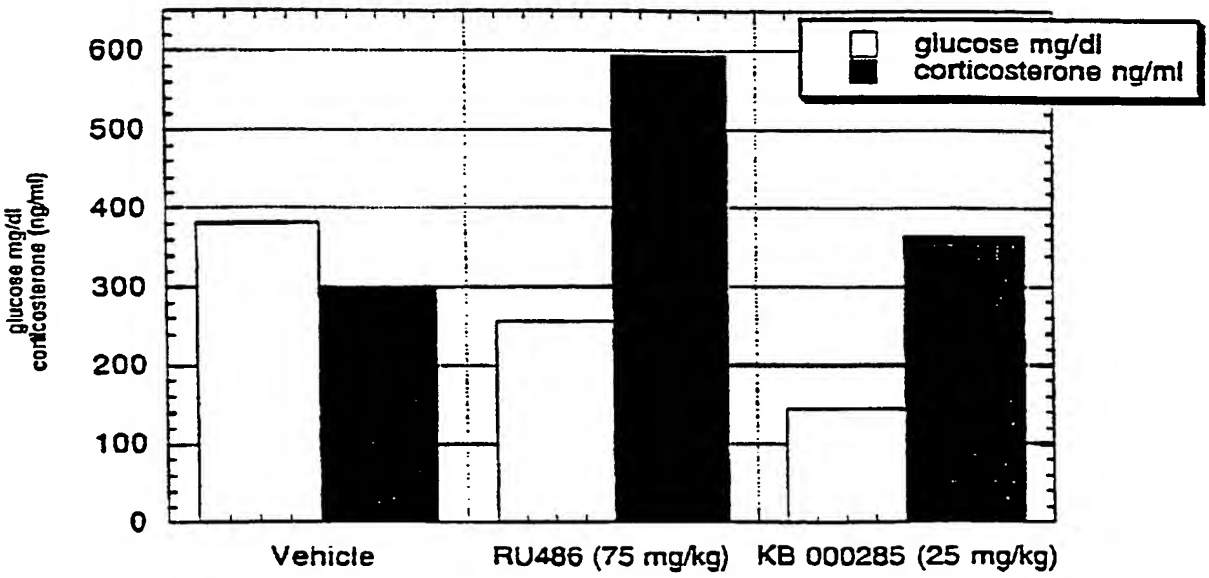


Fig3



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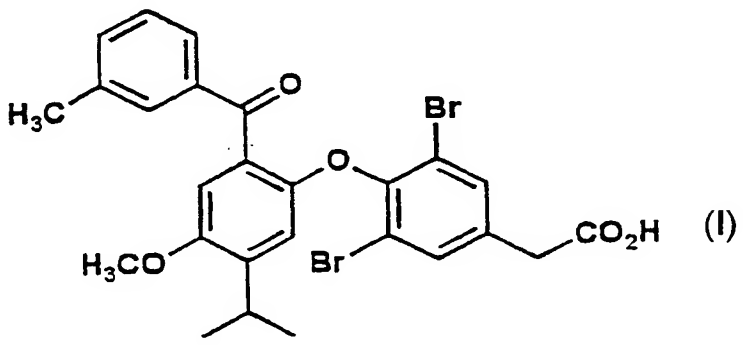
(54) Title: LIVER-SELECTIVE GLUCOCORTICOID ANTAGONIST FOR TREATING DIABETES



(I)

(57) Abstract: Use of a liver-selective glucocorticoid antagonist, preferably the compound having formula (I) in the preparation of a pharmaceutical composition for the treatment of diabetes. A composition for the treatment of diabetes containing such a glucocorticoid antagonist, and a method of treating diabetes using the composition.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GETTYS ET AL.: "Ru-486 (mifepristone) ameliorates diabetes but does not correct deficient beta-adrenergic signalling in adipocytes from mature C57Bl/6J-ob/ob mice" INT. J. OBESITY, vol. 21, no. 10, 1997, pages 865-873, XP002117766 *see in particular the abstract;and Table 1 (p.867) * ---	1-4,6,10
A	CHASSEROT-GOLAZ S ET AL: "Metabolism and antiproliferative effect of the glucocorticoid antagonist RU38486 in cultured liver and hepatoma cells." JOURNAL OF STEROID BIOCHEMISTRY, (1986 JAN) 24 (1) 423-6. , XP002117767 * see in particular the abstract; Fig. 1 * ---	10,12,13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 October 1999	25/10/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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PCT/IB 99/01175

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 374 148 A (BELLETIRE JOHN L) 15 February 1983 (1983-02-15) *see col.1, line 54 - col.2, line 31; formula III *	5,7,11
P,X	WO 98 27986 A (ZYMOGENETICS INC) 2 July 1998 (1998-07-02) * see in particular Tables I & 2 (pages 8,11); page 3, line 15 - page 4 *	1-4,6,10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir ational Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 4530919 A	23-07-1985
WO 9827986 A	02-07-1998	AU 5729098 A	17-07-1998